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EVALUATION OF EFFECTS OF AZILSARTAN MEDOXOMIL AND EPLERENONE ON CLINICAL-HEMODYNAMIC AND SOME NEUROHUMORAL FACTORS IN TREATMENT OF DIFFERENT HEMODYNAMIC PHENOTYPES OF CHRONIC HEART FAILURE

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ABSTRACT

The aim of the study was to evaluate effects of angiotensin (AT) II AT_1 – receptor antagonist representative azilsartan medoxomil and mineralocorticoid receptor antagonist eplerenone to clinical-hemodynamic indexes and serum levels of gelectin-3 and aldosterone in different hemodynamic phenotypes of chronic heart failure patients. The study involved 108 CHF patients: the 1st group consisted of 36 patients with reduced LVEF (LVEF<40%), the 2nd group - 34 patients with intermediate LVEF (LVEF 41 – 49%) and the 3rd group consisted of 38 CHF patients with preserved LVEF (LVEF>50%). Referent serum levels of fibrosis biomarkers were as following: G-3 - 8,6 [3,7;11,7] ng/ml, aldosterone - 86,8 [47,8;199,1] pg/ml. They were administered 40-80mg of azilsartan medoxomil and 25-50mg of eplerenone as a basis therapy for six months. In CHF patients serum levels of G-3 and aldosterone were initially higher compared to control group. Particularly, they were respectively 2,1 and 5,1 times higher in the 1st group patients; 2,2 and 6,2 times in the 2nd; 2,6 and 6,6 times in the 3rd group. After six months of basis treatment, consisting of azilsartan medoxomil and eplerenone combination there was reliable decrease in serum levels of G-3 and aldosterone. In the first group decrease was respectively 9, 1% and 14,2%, in the 2nd 12,4% and 18,6%, in the 3rd group 16,1% and 22,5%. This in turn led to regression of LV remodeling and TBF indexes: in the 1st group LV EDV decreased by 7,4%, ESV by 13,5%, while LVEF increased by 8,5%. In the 2nd group LV EDV decreased by 10%, ESV by 16,6%, while LVEF increased by 7,6%. In the 3rd group decreased by %, ESV decreased by 5,3%, while LVEF increased by 4,1% LV EDV by 1,5%. In patients of the 2nd and 3rd groups LVRWT and LVMI reliably decreased respectively by 4,6% and 2,0%; 6,5% and 3,8% after the treatment. In CHF patients with intermediate and preserved LVEF statistically significant increase of fibrosis markers such as G-3 and aldosterone compared to CHF patients with reduced LVEF, as well as finding of concentric remodeling and hypertrophy of LV indicates increased accumulation of excess collagen in extracellular matrix, myocardial stiffening and intensiveness of fibrosis processes. Concordance between decrease of fibrosis markers and regression of LV remodeling and TBF measurements, and improvement of clinical condition and life quality of and tolerance to physical stress of the patients indicates diminished amount of fibrosis in myocardim. which in turn suggests that combined use of azilsartan medoxomil and eplerenone in treatment of CHF patients would be more prudent.

KEYWORDS: chronic heart failure, galectin – 3, aldosterone, fibrosis markers, azilsartan medoxomil, eplerenone *a.qurbonov@apgmu.uz.*

INTRODUCTION

Chronic heart failure (CHF) is on the pressing problems of modern cardiology. Explicit manifestation of disease symptoms is often mean final and irreversible stages of the disease pathogenesis. Therefore, early diagnosis and administration of effective treatment before manifestation of clinical signs of the disease is very important in modern medicine.[3,12]

Implementation of early detection methods of myocardial fibrosis, which is one of the key mechanisms of CHF, plays an important role in ensuring the effectiveness of antifibrotic treatment.[5] The most accurate method of myocardial fibrosis detection is myocardial biopsy. However, the method is invasive and traumatic, it may be inconvenient to the patient, and in 0, 6 - 0,8% of procedures complications may occur. Moreover, uneven distribution of collagen fibers in myocardium may lead to incorrect results of biopsy analysis.[39] Therefore, use of non-invasive methods in diagnosis of myocardial fibrosis in CHF would be expedient.[25]

In recent years, number of biologic markers have been recommended for use in detection of myocardial fibrosis. One of such biomarkers is galectin - 3 (G-3). Number of conducted studies found that in CHF patients serum G-3 activity is interdependent with miocardial hypertrophy, it stimulates macrophage migration, fibroblast proliferation and fibrosis in cardiac remodeling, and that it is important in predicting progression and unfavorable outcomes of the disease.[15,18] Its role as an intermediate mediator in aldosterone induced perivascular fibrosis in atherosclerosis and diabetes mellitus has been recently discovered.[21,31] Nowadays G-3 is viewed as biomarker of myocardial fibrosis and cardiac remodeling, it has been recommended in clinical use to diagnose, evaluate its progress, treatment monitoring and predict unfavorable outcomes of CHF. [3,6,7,9,14,18,26,30]

Indeed, as problems concerning emergence and progress of CHF are investigated, new questions are coming into being. One of such questions is how myocardial fibrosis, which leads to unfavorable outcomes, be prevented or be dealt with? [11,16] Fibrogenesis is a complex process, where number of factors participate. One of the most important factors is aldosterone. In CHF patients, regardless of disease etiology, secondary hyperaldosteronism is observed. In emergence of the secondary hyperaldosteronism cardiac changes in liver, such as slowing and decreasing of the hormone clearance, may be just as important as activation of components of renin – angiotensin – aldosterone (RAA) system. [4,27] Aldosterone's influence on myocardium was discovered after mineralocorticoid receptors on cardiomyocytes were found.[4,10,12] The secondary hyperaldosteronism causes hypokalemia, hypernatremia, hypervolemia, edema arterial hypertension in organism, which in turn may lead to structural changes in cardiovascular system, including hypertrophy of cardiomyocytes, fibroblast proliferation and increased collagen synthesis. As a result, perivascular and diffuse interstitial fibrosis in myocardium, reduction of its compensatory reserves, life threatening arrhythmias, disease progression, sudden death may occur.[4,28]

Limiting the secondary hyperaldosteronism, which play important role in CHF progress and unfavorable outcomes, or elimination of its causing factors leads to slowing of fibrosis process and stabilization of the disease course. Many clinical trials devoted to study effects of standard medication on CHF pathogenesis found, that use of mineralocorticoid receptor antagonists group (MKRA) medications in addition to antagonists of RAA system and β-blockers in progressed stages of the disease can lead to decrease of the secondary hyperaldosteronism and overall death rate. [12,33,35,38] But in these studies effect of the medication on galectin-3 levels in CHF is not given.

Considering these, we set the aim of our study as following: evaluation of angiotensin (AT) II AT_1 – receptor antagonist representative Azilsartan Medoxomil and MKRA representative eplerenone on serum galectin-3 and aldosterone levels and hemodynamic indexes of different hemodynamic phenotypes of chronic heart.

MATERIALS AND METHODS.

In the study 108 CHF patients were involved. Diagnosis of CHF was made based on patient complaints, history, physical examination, laboratory and imaging investigations using European Society of Cardiology guidelines for the diagnosis and management of CHF (2016) criteria. Functional class of the disease was determined by 6 minute walking test (6MWT) using New York Heart Association classification(1964). Patients were divided into three groups according to their hemodynamic condition and echocardiography (EchoCG) results: the first group consisted of 36 CHF patients with reduced LVEF (LVEF < 40%) (18 - CHF II FC, average age 62,3±1,2 years old, 6 men and 12 women; 18 - CHF III FC, average 63,5±2,3 years old, 9 men and 9 women), the second group consisted of 34 CHF patients with intermediate LVEF (LVEF, 41 - 49%) (16 - CHF II FC, average 62,8±1,7 years old, 12 men and 4 women; 18 - CHF III FC, average age 64,4±1,8 years old, 14 men and 4 women), the third group consisted of 38 CHF patients with preserved LVEF (LVEF > 50%) (20- CHF II FC, average age 64,4±1,3 years old, 8 men and 12 women; 18 - CHF III FC, average 63,6±0,9 years old, 7 men and 11 women). In all involved patients CHF was caused by CHD and essential hypertension. Among the 1st group patients 14 (38,8%) had MI within six months, 4 (11,1%) had coronary bypass or stenting, 10 (27,8%) had rythm disorders and blockades, 1 (2,8%) had heart aneurism after MI. In this group 5 (13,9%) had second type deabetes, 7 (19,4%) had obesity, and 3 (8,3%) had anemia as comorbidities. Among the 2nd group patients 27 (79,4%) had MI within six months, 6 (17,6%) had coronary bypass or stenting, 8 (23,5%) had rythm disorders and blockades, 7 (20,6%) had heart aneurisma after MI. In this group 6 (17,6%) had second type deabetes, 8 (23,5%) had obesity, and 4 (11,8%) had anemia as comorbidities. Among the 3rd group patients 9 (23,7%) had MI within six months, 1 (2,6%) had coronary bypass or stenting, 10(26,3%) had rythm disorders and blockades, 1 (2,6%) had heart aneurisma after MI. In this group 8 (21,1%) had second type deabetes, 9 (23,7%) had obesity, and 3(7,9%) had anemia as comorbidities.

Patients involved in our study received from standard CHF treatment recommended in European Society of Cardiology guidelines (2016) (ACE inhibitor or ARA, β – blocker, MKRA) ARA representative Azilsartan Medoxomil and MKRA representative – eplerenone together for 6 months in order to prevent CHF progression and to limit fibrosis process. The 1st group patients received 40 mg of Azilsartan Medoxomil twice a day, the 2nd and 3rd group patients received 40mg of the medicine and its dose was doubled to 80 mg when it was possible. Clinical condition of the patients, heart beat

rate, blood pressure and the medicines side effects were taken into consideration in determining the dose of Azilsartan Medoxomil. When patients had arterial hypotension or other side effects, initial dose of Azilsartan Medoxomil was lowered. Patients of all three groups received 25 – 50 mg of eplerenoneни daily (medium dose of the drug was 37, 4±5, 7 mg). Clinical characteristics of chronic heart failure patients in our study is given in Table 1.

Table: 1. Clinical characteristics of chronic heart failure patients.

Index	Total, n=108	CHF with reduced LVEF, 1st group n=36	CHF with intermediate LVEF, 2nd group, n=34	CHF with preserved LVEF, 3rd group, n=38
Age, years	62,3±1,4	63,0±1,6	63,2±1,3	64,0±1,4
Sex, men/women	56/52	15/21	26/8	15/23
Body mass index, kg/m2	30,8±0,9	29,9±1,0	31,9±1,0	30,5±0,8
Duration of CHF, years	4,2±2,4	4,3±2,6	4,2±2,5	4,1±1,7
Post infarct cardiosclerosis	50(46,3%)	14 (38,8%)	27 (79,4%)	9 (23,7%)
Coronary bypass / stenting	11(10,2%)	4 (11,1%)	6 (17,6%)	1 (2,6%)
Rhythm disorders and blockades	31(28,7%)	10 (27,8%)	8 (23,5%)	13(34,2%)
Heart aneurism	9 (8,3%)	1 (2,8%)	7 (20,6%)	1 (2,6%)
Left ventricle ejection fraction, %	49,8±0,3	36,4±0,4	46,0 ±0,3	60,9 ±0,5
Evaluation of clinical state scale, point	6,6±0,3	6,6±0,3	6,8±0,3	6,6±0,2
Quality of life (Minnesota Living with Heart Failure (MLHF)), point	51,4±1,4	48,7±1,6	52,0±1,7	53,9±1,3
6 minute walking test (6MWT)	283,4±9,2	280,0±12,6	291,4±14,1	295,5±12,4
Comorbidities:				
Diabetes mellitus	34(31,5%)	13(36,1%)	12 (35,3%)	9 (23,7%)
Obesity	34 (31,5%)	12(33,3%)	13 (38,2%)	9 (23,7%)
Anemia	20 (18,5%)	4 (11,1%)	9 (26,5%)	7 (18,4%)
Galectin – 3, ng/ml	20,7±1,1	18,7±1,2	19,3±1,2	22,3±0,9
Aldosterone, pg/ml	521,8±14,7	445,9±20,3	535,7±13,5	570,5±11,3
Treatment:				
ARA,(%)	108 (100)	36 (100)	34 (100)	38 (100)
β - blocker, (%)	90 (83,3)	30(83,3)	32 (94,1)	28 (73,4)
MKRA, (%)	108 (100)	36 (100)	34 (100)	38 (100)
Statins, (%)	64(59,3)	21 (58,3)	18 (52,9)	25(65,8)

Note: LVEF – left ventricle ejection fraction, ARA – angiotensin II AT_1 – receptor antagonist, β – blocker – beta – adrenoblocker, MKRA – mineralocorticoid receptor antagonist.

In all patients of the study following were conducted before and six months after the treatment: general blood and uruine analysis, blood sugar analysis; biochemical analysis of liver transferases, bilirubin, uric acid, creatinine, lipid spectrum of the blood, coagulogramm; immune ferment analysis: serum G-3 and aldosterone; and instrumental investigations: electrocardiography (ECG), ECG Xolter monitoring, echocardiography (EchoCG), chest X-ray (cardiothoracic index).

All immune ferment analyses were conducted in Immunopathology laboratory of specialized Pediatrics research center of Ministry of Healthcare of Republic of Uzbekistan. Serum G-3 levels were measured using human Galectin-3 ELISA reagent (Germany); aldosterone levels - using Aldosterone ELISA reagent (Canada); Reference level of serum G-3 in the study was - 8,6 [3,7; 11,7], that of aldosterone was 86,8 [47,8; 199,1].

EchoCG was made using transthoracic access in PHILIPS Affiniti 70 (Netherlands) device, frequency - 5-1 MHz. During echocardiography M and B modes were used and recommendations of American Society of Echocardiography (ASE,2015) were followed. During investigation following were measured: end diastolic and end systolic size of LV (EDS and ESS), end diastolic and end systolic volume of LV (EDV and ESV), posterior wall thickness of LV (LVPWT) and interventricular septal thickness (IVST), left atrium (LA) size, left ventricle ejection fraction (LVEF), stoke volume (SV), left ventricular mass (LVM) using Devereux R.B. formula - LVM =0,8 [1,04 (EDS + LVPWT + IVST)3 – EDS3] + 0,6 g, LVM index (LVMI) using LVMI = LVM/S (body), g/m2 formula. When LVMI values were ≥115g/m^2 in men and ≥95g/m^2 in women it was considered as LV hypertrophy. Remodeling of LV myocardium was determined based on relative thickness of its wall (LVRWT = IVST + LVPWT / EDS).

Structural remodeling of myocardium was divided into following groups (A. Ganau, 1992): Normal geometry of LV - LVMI=N, LVRWT<0, 42; concentric hypertrophy LVMI>N, LVRWT>0, 42; concentric remodeling LVMI =N, LVRWT >0, 42; eccentric hypertrophy LVMI >N, LVRWT <0, 42.

Diastolic dysfunction of LV was diagnosed based on values of transmitral blood flow (TBF) in pulmonary veins in Doppler EchoCG. In evaluating TBF early (E) and end diastolic filling (A) of LV, ratio between them (E/A), isovolumetric relaxation of LV (IVRT), slowed early diastolic filling time of LV (DT) were measured. LV diastolic dysfunction was evaluated as 3 types: Type I – impaired relaxation of LV, Type II – pseudo normal and Type III - restrictive. In Type I - E/A ≤ 1, IVRT>110 ms and DT>240 ms; in Type III - E/A > 1, 6, IVRT< 90 ms and DT<150 ms (Nagueh SF., 2009). The gathered data was compared with control group results consisting of 20 healthy volunteers.

Data analysis. For data processing MS Excel (2013) computer program was used. Arithmetic mean and standard deviation (M±m) of all data in following tables were calculated. Student's paired and unpaired t-tests were used to determine significance of difference between groups. Chi square tests were used to determine qualitative difference between groups. Correlation analysis was done using Pearson's correlation coefficient and confidence tables.

RESULTS

Before the treatment serum levels of G-3 and aldosterone that indicate disbalance of collagen in extracellular matrix, was higher in all three groups of CHF patients compared to control group, namely in the 1st group patients it was respectively 2,1 and 5,1; in the 2nd groupда 2,2 and 6,2; in the 3rd group 2,6 and 6,6 times higher. After six months of combined basis therapy with Azilsartan Medoxomil and eplerenone there was reliable decrease in serum G-3 and aldosterone levels. Namely, there was decrease in the 1st group respectively from 18,7±1,2 to 17,0±1,1 ng/ml and from 445,9±20,3 to 382,6±18,4 pg/ml (p<0,05); in the 2nd group from 19,3±1,2 to 16,9±1,1 ng/ml (p<0,01) and from 535,7±13,5 to 436,1±12,2 pg/ml (p<0,05); in the 3rd group from 22,3±0,9 to 18,7±0,8 and from 570,5±11,3 to 442,1±10,8 pg/ml (p<0,01). Decrease of these fibrosis markers as a result of treatment indicates statistically significant regression of left ventricular remodeling in CHF patients (Table 2).

Table 2: Dynamics of left ventricular remodeling and levels of neurohumoral factors in chronic heart failure patients after the treatment.

Index	1st group, CHF with reduced LVEF, n=36		2nd group, CHF with intermediate LVEF, n=34		3rd group, CHF with preserved LVEF, n=38	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
EDV, ml	219,7±6,5	203,5±5,8*	187,9±10,4	169,1±9,8*	130,3±2,7	132,2±2,4
ESV, ml	140,4±5,0	121,4±4,9**	101,2±6,2	84,4±5,8**	49,8±1,3	47,2±1,2
IVST, mm	10,6±0,1	10,5±0,1	10,7±0,3	10,3±0,2*	12,5±0,2	12,2±0,1**
LVPWT, mm	11,3±0,2	11,2±0,2	12,1±0,2	12,0±0,2	13,6±0,2	13,2±0,1**
LVEF, %	36,4±0,4	39,5±0,3**	46,0±0,3	49,5±0,3**	60,9±0,5	63,4±0,6**
LVMI, g/m^2	267,7±9,1	265,2±8,7	224,7±8,7	220,3±7,9*	193,8±6,5	186,4±5,7**
LVRWT	0,34±0,01	0,34±0,01	0,43±0,01	0,41±0,01*	0,46±0,02	0,43±0,1**
G-3, ng/ml	18,7±1,2	17,0±1,1*	19,3±1,2	16,9±1,1**	22,3±0,9	18,7±0,8**
Aldosterone, ng/ml	445,9±20,3	382,6±18,4*	535,7±13,5	436,1±12,2*	570,5±11,3	442,1±10,8**

Note. * - reliability of differences, p < 0,05;
** - reliability of differences, p < 0,01.
EDV – end diastolic volume, ESV – end systolic volume, LVMI – left myocardial mass index, LVRWT – Left ventricular relative wall thickness, IVST – interventricular septal thickness, LVPWT – left ventricular posterior wall thickness, LVEF – left ventricle ejection fraction, G-3 – galectin -3.

In all patients of the 1st group patients LV remodeling was of eccentric type, after the treatment there was reliable decrease of LV EDV from 219,7±6,5 to 203,5±5,8 ml (p<0,05) and of LV ESV from 140,4±5,0 to 121,4±4,9 ml (p<0,01), additionally LVEF increased from 36,4±0,4 to 39,5±0,3 % (p<0,01). Among the 2nd group patients 16 had concentric LV hypertrophy, while 18 had eccentric LV hypertrophy. After the treatment LV EDV reliably decreased from 187,9±10,4 to 169,1±9,8 ml (p<0,05) and LV ESV from 101,2±6,2 to 84,4±5,8 ml (p<0,01), while LVEF increased from 46,0±0,3 to 49,5±0,3% (p<0,01). Among the 3rd group patients 34 had concentric LV hypertrophy, while 4 had eccentric LV hypertrophy. After the treatment LV EDV increased from 130, 3±2, 7 to 132, 2±2, 4 ml and LV ESV decreased from 49, 8±1, 3 to 47, 2±1, 2 ml. In these patients LVEF reliably increased from 60, 9±0, 5 to 63, 4±0, 6 % (p<0,01).

As known, In CHF patients LV hypertrophy is one of the factors that contribute to development of unfavorable outcomes of the disease in CHF patients. In the 1st group patients of the study, although there was no statistically significant changes in LVRWT, LVPWT and IVST measurements, LVMI decreased from 267,7±9,1 to 265,2±8,7 g/m^2 as a result of the treatment. In the 2nd group patients there was reliable decrease in levels of IVST from 10,7±0,3 to 10,3±0,2mm, LVRWT from 0,43±0,01 to 0,41±0,01, LVMI from 224,7±8,7 to 220,3±7,9 g/m^2 (p<0,05). Даво негизида In the 3rd group patients there was reliable (p<0,01) decrease of IVST from 12,5±0,2 to 12,2±0,1, LVPWT from 13,6±0,2 to 13,2±0,1, LVRWT from 0,46±0,02 to 0,43±0,02 and LVMI from 193,8±6,5 to 186,4±5,7 g/m^2.

Организмдаги Effects of decreased levels of G-3 and aldosterone that indicate the intensiveness of the fibrosis and inflammation processes after the treatment on diastolic dysfunction (DD) of LV was measured using TBF measurements (Table 3).

Table 3: Dynamics of transmitral blood flow in chronic heart failure patients after the treatment.

Index	1st group, CHF with reduced LVEF, n=36		2nd group, CHF with intermediate LVEF, n=34		3rd group, CHF with preserved LVEF, n=38	
	Before treatment	After treatment	Before treatment	Before treatment	After treatment	Before treatment
E, m/s	0,79±0,01	0,82±0,01*	0,62±0,03	0,64±0,03*	0,62±0,03	0,68±0,03**
A, m/s	0,41±0,01	0,42±0,01	0,75±0,03	0,67±0,03**	0,72±0,03	0,63±0,03**
E/A	1,98±0,07	1,95±0,07	0,93±0,1	0,96±0,1*	0,99±0,1	1,08±0,1**
IVRT, m/s	90,8±3,4	88,8±3,3	103,8±0,4	96,01±0,3*	117,2±1,4	100,8±1,3**
DT,m/s	156,1±3,8	154,7±3,6	225,1±2,8	212,9±2,6*	245,6±2,2	218,6±2,1**

Note. * - reliability of differences, p < 0,05;
** - reliability of differences, p < 0,01.
E – early diastolic relaxation of LV; A - late diastole of LV; E/A – ratio of early diastolic relaxation and late diastole of LV; IVRT – isovolumic relaxation time; DT – slowing of early diastolic dilation of LV.

In CHF patients with reduced LVEF early diastolic relaxation of LV (E) increased by 3, 8% after the treatment, while there was no statistically significant change in other indicators of TBF. 21 CHF patients with intermediate LVEF had impaired relaxation type of LV DD, 10 had pseudo normal, and 3 had restrictive LV DD. After the treatment, increase of E from 0,62 [0,32; 1,0] to 0,64 [0,39; 0,95], of E/A ratio from 0,93 [0,43; 3,22] to 0,96 [0,49; 3,14], decrease of late diastole of LV (A) from 0,75 [0,31; 1,03] to 0,67 [0,38; 0,97], of isovolumic relaxation time (IVRT) to 7,5%, and of slowing of early diastolic dilation of LV (DT) to 5,4% was found. 24 CHF patients with preserved LVEF had impaired relaxation type of LV DD, 9 had pseudo normal, and 5 had restrictive type LV DD. After the treatment, increase of E from 0,62 [0,29; 1,14] to 0,68 [0,32; 1,08], of E/A ratio from 0,99 [0,51;3,08] to 1,08 [0,49; 3,02], decrease of late diastole of LV (A) from 0,72 [0,24; 1,01] to 0,63 [0,28; 0,95], of isovolumic relaxation time (IVRT) to 14%, and of slowing of early diastolic dilation of LV (DT) to 11% was found. Which in turn indicate, that relaxation of LV was improved because of reduction of fibrosis processes in myocardium.

When TBF measurements were studied in relation to LV DD types of the groups, following was found: all patients of the 1st group had restrictive type LV DD, and after the treatment only minor increase in early diastolic relaxation of LV (3,8%). 3 patients of the 2nd group and 5 patients of the 3rd group also had restrictive type LV DD, after the treatment there was no statistically significant changes in TBF measurements. In CHF patients of these groups with impaired relaxation of LV and pseudo normal type of LV DD following changes occurred after the treatment (Tables 4 and 5).

Table 4: Dynamics of transmitral blood flood measurements in relation to types of LV diastolic dysfunction in chronic heart failure patients with intermediate LVEF after the treatment.

Index	Impaired relaxation of LV n=21		Pseudo normal n=10	
	Before treatment	After treatment	Before treatment	After treatment
E, m/s	0,50 ±0,02	0,61±0,01***	0,81±0,02	0,83±0,02
A, m/s	0,85±0,02	0,76±0,01***	0,66±0,03	0,65±0,03
E/A	0,59±0,02	0,8±0,02***	1,24±0,05	1,28±0,04
IVRT, m/s	118,9±2,3	103,6 ± 2,1**	96,4± 1,2	94,7 ± 1,1
DT, m/s	248,4±3,1	224,8±2,6**	147,3±0,9	151,6±1,1

Note. * - reliability of differences, $p < 0,05$;
** - reliability of differences, $p < 0,01$.

Table 5: Dynamics of transmitral blood flood measurements in relation to types of LV diastolic dysfunction in chronic heart failure patients with preserved LVEF after the treatment.

Index	Impaired relaxation of LV n=24		Pseudo normal n=9	
	Before treatment	After treatment	Before treatment	After treatment
E, m/s	0,51 ±0,03	0,61±0,03***	0,78±0,07	0,79±0,06
A, m/s	0,79±0,03	0,7±0,03***	0,7±0,07	0,71±0,07
E/A	0,65±0,03	0,87±0,03***	1,14±0,05	1,1±0,04
IVRT, m/s	122,4±2,7	108,4 ± 2,5**	88,6± 2,6	86,2 ± 1,9
DT, m/s	253,6±2,1	226,6±1,8**	143,2±1,8	146,6±2,0

Note. * - reliability of differences, $p < 0,05$;
** - reliability of differences, $p < 0,01$.
*** - reliability of differences, $p < 0,001$.

In I type LV DD patients of the 2nd and 3rd groups after administration of azilsartan medoxomil and eplerenone for six months following was found: early diastolic relaxation of LV increased respectively to 22,0 and 19,6% ($p<0,001$), in late diastole of LV participation of atriums decreased respectively to 11,6 and 11,4% ($p<0,001$). As a result, ratio of these two phases of diastolic relaxation (E/A) rose respectively to 35,6 and 33,8% ($p<0,001$), there was decrease in isovolumic relaxation time (IVRT) to 12,9 and 11,4 %, and in slowing of early diastolic dilation of LV (DT) to 9,5 and 10,7 % га камайди ($p<0,01$). In patients with pseudo normal type of LV DD of the study, only in CHF patients with intermediate LVEF E increased by 2, 4 %, while there was no statistically significant in other indicators of TBF.

Significant improvement occurred in clinical conditions, life quality and tolerance to physical stress of patients after the treatment (Table 6).

Table 6: Dynamics of indicators of clinical condition and life quality of chronic heart failure patients after the treatment.

Index	1st group, CHF with reduced LVEF, n=36		2nd group, CHF with intermediate LVEF, n=34		3rd group, CHF with preserved LVEF, n=38	
	Before treatment	After treatment	Before treatment	Before treatment	After treatment	Before treatment
Evaluation of clinical state scale, point	6,6±0,3	5,2±0,2*	6,8±0,3	5,0±0,3*	6,6±0,2	4,7±0,2**
Quality of life (Minnesota Living with Heart Failure (MLHF)), point	48,7±1,6	37,8±1,4*	52,0±1,7	36,3±1,7*	53,9±1,3	36,8±1,1**
6 minute walking test (6MWT)	280,0±12,6	332,4±9,4*	291,4±14,1	373,0±14,1*	295,5±12,4	381,2±10,5**

Note. * - reliability of differences, $p < 0,05$;
** - reliability of differences, $p < 0,01$.

Evaluation of clinical state scale points of patients (В.Ю.Мареев modification, 2000) reliable decreased in the 1st group from 6,6 to 5,2; in the 2nd group from 6,8 to 5,0; in the 3rd group from 6,6 to 4,7 points. Their quality

of life also improved. MLHF points reliable decreased in all thee groups from 48,7 to 37,8; from 52,0 to 36,3 and from 53,9 to 36,8 points respectively. Patients' tolerance to physical stress was measured using 6MWT, and it reliably increased in the 1st group from 280 to 332,4; in the 2nd group from 291,4 to 373,0; and in the 3rd group from 295,5 to 381,2 meter as a result of the treatment. These positive changes resulted in reliable improvement of the functional classes of CHF from 2,5 to 2,3 in the 1st group; from 2,6 to 2,2 in the 2nd group; from 2,5 to 2,1 in the 3rd group.

DISCUSSION

According to current views on CHF pathogenesis, activation of sympatho-adrenal, renin – angiotensin – aldosterone (RAA), endothelia and immune - inflammation systems plays an important role in development of myocardial fibrosis which is crucial in cardiac remodeling in different hemodynamic phenotypes of the disease.[2,8,13]

In modern medical practice, angiotensin converting ferment inhibitor (ACE inhibitor) or angiotensin (AT) II AT_1 - receptor antagonist (ARA), beta – adrenoblocker (β-blocker) and MKRA are widely used in treatment of CHF to positively affect the course and outcomes of the disease.[1,11,12,17,33,35] ACE inhibitors and ARAs negate the negative effects of ATII, while β – blockers decrease the secretion of renin and ATI. But when antagonists of RAA system are used for long time, "aldosterone escape" phenomenon develops, which is explained by synthesis of ATII and aldosterone through channels independent of ACE. Currently, this problem is solved by administering MKRAs.[4,10,13,29] Such a three component blockade of RAA system is considered the main pathogenic treatment of CHF with reduced LVEF, and it reduces mortality in all functional classes of the disease to 45%.[11,35] Use of ARAs in different populations of CHF patients and their cardioprotective effects were proved in large clinical studies as CHARM, Val–HeFT, SOLVD, ELITE II, HEAAL, VALIANT, ONTARGET.[11] These studies found, that ARAs were not only alternative to ACE inhibitors, but also were equal or superior to the letter because of the former's pleotropic effect.[32,34] Pleotropic and cardioprotective effects of ARAs is manifested by decreased proliferation of smooth muscle cells, restoration of endothelial cells, slowed degradation of bradykinin degradation and consequent increase in NO and prostacyclin production, vasodilation, activation of antioxidant defense system, and slowed remodeling of left ventricle through stimulation of AT_2 - receptors. By affecting the above-mentioned aspects of the disease pathogenesis the medication causes positive results in CHF patients. Studies found that there was positive effects to the course of numerous comorbidities through increased sensitivity of tissues to insulin, reduction of fat tissue in organism and additional metabolic effects, as well as absence of "aldosterone escape" phenomenon when ARAs were used.[19,22,24] Indeed, if we consider, that CHF with preserved and preserved LVEF often combines with number of comorbidities, theoretically, these medications can be named as first choice in treatment of above-mentioned phenotypes of the disease. According to current literature review, Use of ARA representatives in combination with MKRA in pathogenetic treatment of CHF leads to stabilization of the disease course, prevention of unfavorable outcomes and and reversion of fibrosis processes in cardiovascular system.[5,8,11,12]

Before the treatment with azilsartan medoxomil and eplerenone for six months, in all patients of three groups G-3 and aldosterone levels that indicate disbalance of collagen metabolism in organism were higher compared to the control group respectively 2,1 and 5,1 times in the 1st group; 2,2 and 6,2 times in the second; 2,6 and 6,6 times in the 3rd group. According to studies, fibrosis processes in myocardium varies quantitatively and qualitatively in different hemodynamic phenotypes of CHF.[11,16] In or study too, patients' levels of fibrosis markers increased differently, and the results were higher in the 2nd and the 3rd group compared to the 1st group, which in turn indicate in the last group fibrosis process manifested more strongly. After the treatment serumдаги levels of G-3 and aldosterone reliably decreased respectively 9, 1 and 14, 2% in the 1st group, 12, 4 and 18,6% in the second, 16,1 and 22,5% in the 3rd and led to regression of LV remodeling measures. Particularly, in the 1st group patients LV EDV decreased by 7, 4%, ESV and decreased by 13, 5%, while LVEF increased by 8, 5%. In the 2nd group LV EDV decreased by 10 %, ESV decreased by 16, 6 %, and LVEF increased by 7, 6%. Higher levels of fibrosis markers in the 3rd group patients compared to other groups means that myocardium, initially having normal measures of systolic and diastolic volumes of LV, had stiffened as a result of clearly manifested fibrosis process. Decreased levels of fibrosis markers as a result of the treatment allowed ESV to decrease to 5, 3%, LV EDV and LVEF to increase to 1, 5%, and 4,1% respectively. These indicate that relaxation and contraction of LV had improved in patients of this group as a result of diminished fibrosis.

In CHF patients hypertrophy of LV is one of the factors which lead to development of unfavorable outcomes of the disease, and its regression has a positive effect on the disease course. According to results of the study, in the 1st group patients there was no statistically significant changes in LVRWT, LVPWT and IVST. In the 2nd and the 3rd group group patients decrease of serum fibrosis markers as a result of the treatment led to reliable decrease of LVRWT and LVMI to 4,6% and 2,0%; 6,5% and 3,8% respectively. This in turn proves, that in course of CHF increased mass and width of myocardium is not only caused by hypertrophy of cardiomyocytes, but also accumulation of abnormal amounts of collagen in interstitial tissue, and that decreased levels of these indexes in CHF patients with intermediate and preserved LVEF after the treatment indicate reduction of fibrosis levels in myocardium.

In patients of the study, who had restrictive characteristics of TBF measurements, LV remodeling was of eccentric type and was caused by experienced myocardial infarction, cardiac aneurisms, various rhythm disorders and decompensation of different comorbidities. In those patients early diastolic relaxation of LV increased by 3, 8%, while there was no statistically reliable change in other TBF measurements. In CHF patients with intermediate and preserved LVEF there was positive changes only in I type of LV DD. We explained this result in following way: regression of myocardial fibrosis created better conditions to relaxation of LV during early and late diastole. Among patients with pseudo normal type of LV DD increase of E by 2, 4% occurred only in the 2nd group, there was no other statistically significant changes. This can be explained by different levels of fibrosis depending on duration and stage of the disease as well as irreversible changes caused by neurohumoral factors.

Indeed, functional and morphological changes in different hemodynamic phenotypes of CHF is tightly interrelated with course and outcomes of the disease.[23] In this grave complication, level of myocardial damage is directly dependent on oxygen shortage of tissues and organs, as well as fibrosis processes caused by hemodynamic and neurohumoral disorders.[36] By detecting processes of fibrosis early and affecting neurohumoral factors activating it, CHF can be successively controlled.[37]

Based on data collected from our study, we draw following conclusion. In different hemodynamic phenotypes of chronic heart failure, diffusion of oxygen in myocardium worsens because of myocardial fibrosis induced dysfunction of cardiomyocytes and interstitial tissue and reduced number of capillaries. As e result, tissue hypoxia accelerates, systolic and diastolic function of the heart deteriorates, and various types of cardiac remodeling occurs in different hemodynamic phenotypes of CHF. In different hemodynamic phenotypes of the disease amount of fibrosis varies qualitatively and quantitatively, thus differentiated approach increases effectiveness of pathogenetic treatment of the disease.[5,7,16]

In CHF patients with intermediate and preserved LVEF statistically significant increase of fibrosis markers such as G-3 and aldosterone compared to CHF patients with reduced LVEF, as well as finding of concentric remodeling and hypertrophy of LV indicates increased accumulation of excess collagen in extracellular matrix, myocardial stiffening and intensiveness of fibrosis processes.

Decreased levels of integral part of RAA system (aldosterone) and marker of collagen metabolism disorder in organism (galectin – 3) in patients as a result of treatment and its concordance with regression of LV remodeling and TBF measurements, and improvement of clinical condition and life quality of and tolerance to physical stress of the patients indicates diminished amount of fibrosis in myocardium. This in turn suggests that combined use of azilsartan medoxomil and eplerenone in treatment of CHF patients would be more prudent. Based on the study results and taking into account explicit manifestation of fibrosis processes in CHF with intermediate and preserved LVEF it can be said, that combined use of above-mentioned medications in treatment of patients provides positive hemodynamic and neurohumoral as well as cardioprotective effect.

REFERENCES

1. Alyavi A.L., Kamilova U.K., Rasulova Z.D. Chronic heart failure. – Tashkent, 2017; 196.
2. Berezin A.E., Kremzer A.A., Samura T.A. The predictive role of various phenotypes of circulating endothelial-derived microparticles in patients with chronic heart failure: results of prospective study // Heart and vessels, 2015; 1: 22 – 30.
3. Berezin A.E. Biological markers in chronic heart failure: expectations, reality, prospects // Ukr. J. heart failure, 2013; 1: 5 - 15.
4. Gilyarevsky S.R., Golshmid M.V., Kuzmina I.M. The role of aldosterone receptor antagonists in the prevention and treatment of cardiovascular and renal diseases: reality and prospects // Russian Medical Journal, 2014; 23: 1689 - 1698.
5. Gadaev A.G., Kurbonov A.K. Some new approaches to the development and treatment of chronic heart failure // Medical Journal of Uzbekistan, 2015; 4: 81 - 85.
6. Gyamdzhyan K.A., Kukes V.G., Maksimov M.L. Clinical value of determining galectin - 3 in patients with chronic heart failure // Medical Council, 2017; 7: 63 - 68.
7. Drapkina O.M., Shepel R.N., Deeva T.A., Kaburova A.N. Galectin-3 in patients with left ventricular hypertrophy and metabolic syndrome // Arterial Hypertension, 2018; 24(3): 272 - 280.
8. Drapkina O.M., Palatkina L.O. New emphases on the study of the pathogenesis of chronic heart failure with preserved ejection fraction: focus on inflammatory markers // Rational pharmacotherapy in cardiology, 2014; 10(3): 317 - 321.
9. Karoli N.A., Borodkin A.V., Kosheleva N.A., Rebrov A.P. Prognostic markers for the development of adverse outcomes in patients with chronic obstructive pulmonary disease and chronic heart failure // Kardiologiia., 2018; 58(9): 39 - 47.
10. Karpov Yu. A., Sorokin Ye. V. Mineralocorticoid receptor antagonists in chronic heart failure: indications for use and drug choice in the light of modern knowledge // Atmosphere. Cardiology News, 2015; 1: 21 - 26.
11. Kurbonov A.K. The role of fibrotic processes in chronic heart failure and the optimization of its treatment. Abstract the diss ... of the doctor of philosophy on medical sciences. 14.00.06. – Tashkent, 2018; 51.

12. Mareev V.Yu., Fomin I.V., Ageev F.T. Chronic heart failure. // Journal of heart failure, 2017; 18(1): 3 - 40.
13. Mareev V.Yu., Fomin I.V., Ageev F.T. Clinical recommendations OSSN - RKO - RNMOT. Heart failure: chronic (CHF) and acute decompensated (ODSN). Diagnosis, prevention and treatment // Cardiology, 2018; 58(6): 8 - 158.
14. Medvedeva E.A. Berezin I.I., Schukin Yu.V. Galectin-3, markers of oxidative stress and renal dysfunction in patients with chronic heart failure // Cardiology, 2017; 57(3): 46 - 50.
15. Osipova O.A., Plaksina K.G., Komisov A.A. et al. The pathogenetic mechanisms of participation of myocardial extracellular matrix remodeling of the heart in patients with chronic heart failure // Scientific reports of Belgorod State University. Series: Medicine. Pharmacy, 2015; 22(219): 18 - 25.
16. Solomakhina N. I., Belenkov Yu. N., Varshavsky V. A. Myocardial fibrosis in systolic and diastolic chronic heart failure. - Moscow: Medical practice, 2014; 62.
17. Fomin I.V. Chronic heart failure in Russian Federation: what do we know and what to do // Russian Journal of Cardiology, 2016; 8: 7 - 13. doi: 10.15829 / 1560-4071-2016-8-7-13.
18. Tseluyko V.I., Lozova T.A. Galectin-3 and the state of post-infarction remodeling in patients with right ventricular myocardial infarction on the background of infarction of the posterior wall of the left ventricle // Ukrainian Journal of Cardiology, 2014; 5: 37 - 43.
19. Chazova I.E., Karpov Yu.A., Ostroumova O.D. et al. Azilsartan medoxomil - expanding opportunities to improve blood pressure control // System. Hypertensive, 2014; 3: 95 - 98.
20. Ambrosy A. P.et al. The global health and economic burden of hospitalizations for heart failure // J Am Coll Cardiol, 2014; 63; 1123 - 1133.
21. Calvier L. Galectin-3 mediates aldosterone-induced vascular fibrosis // Atheroscler Thromb Vasc Biol, 2013; 33 (1): 67- 75.
22. Chrysant S.G. Current status of dual renin angiotensin aldosterone system blockade for the treatment of cardiovascular diseases // Am J Cardiol, 2010; 105(6): 849 - 52.
23. Colucci W.S., Braunwald E. Atlas of Heart Failure. – Springer, 5 th. Ed, 2008; 344.
24. Dezsi C.A. The Different Therapeutic Choices with ARBs. Which One to Give? When? Why? // Am J Cardiovasc Drugs, 2016; 16(4): 255 – 66.
25. Gadaev A.G., Kurbanov A.K., Turaqulov R.I. The Urgency of Firotic Processes in Chronic Heart Failure // World Healthcare Providers, 2017; 8(6): 77 – 80.
26. Gehlken C., Suthahar N., Meijers W.C. et al. Galectin-3 in Heart Failure: An Update of the Last 3 Years // Heart Fail Clin, 2018; 14(1): 75 - 92.
27. Guichard J.L., Clark D., Calhoun D.A., Ahmed M.I. Aldosterone receptor antagonists: current perspectives and therapies // Vasc Health Risk Manag, 2013; 9: 321 - 331.
28. Hu L.J., Chen Y.Q., Deng S.B. et al. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis // Br. J. Clin. Pharmacol, 2013; 75: 1202 - 1212.
29. Iqbal J., Parviz Y., Pitt B. et al. Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure //Eur. J. Heart Fail, 2014; 16: 143 - 150.
30. Kurbonov A.K. The value of biological markers in the diagnosis, prediction and evaluation of the effectiveness of treatment of chronic heart failure // Central Asian Journal of Medicine, 2019; 1(9): 65 – 73.
31. Li Y.Y. Myocardial extracellular matrix remodeling in transgenic mice overexpressing tumor necrosis factor alpha can be modulated by antitumor necrosis factor alpha therapy / Li Y.Y., Feng Y.O., Kadokami T. // Proc. Nat. Acad. Sci. USA, 2010; 97: 12746 – 12751.
32. Li E.C., Heran B.S., Wright J.M. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension // Cochrane Database Syst Rev, 2014; (8): CD009096.
33. McMurray J.J., Adamopoulos S., Anker S.D. et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC // Eur J Heart Fail, 2012; 14(8): 803 - 69.
34. Podzolkov V.I., Pisarev M.V. Angiotensin Receptor Blockers with Pleiotropic Properties: a New Standard in Cardiovascular Risk Management and Treatment of Hypertension // Rational Pharmacotherapy in Cardiology, 2017; 13(3): 383-390.
35. Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. // European Heart Journal, 2016; 37(27): 2129 - 200.
36. Rockey D.C. Current and Future Anti–fibrotic Therapies for Chronic Liver Disease // Clin Liver Dis, 2008; 12(4): 939 - 948.
37. TA Wynn. Cellular and molecular mechanisms of fibrosis // J Pathol, 2008; 214: 199 - 210.
38. Van der Meer P., Gaggin H.K., Dec G.W. ACC/AHA Versus ESC Guidelines on Heart Failure: JACC Guideline Comparison // J Am Coll Cardiol, 2019; 73(21): 2756 - 2768.
39. Yilmaz A, Kindermann I, Kindermann M et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences incomplication rate and diagnostic performance // J Circulation, 2010; 122: 900 – 909.